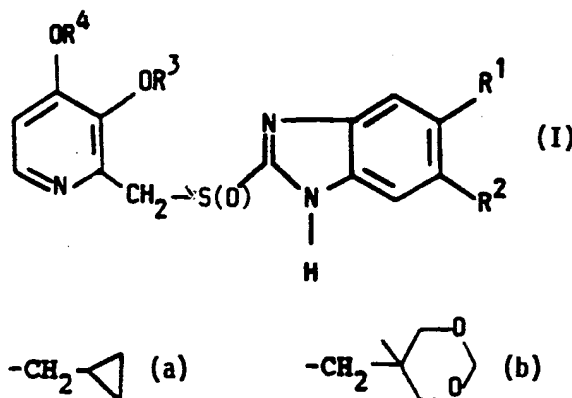




INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁵ : C07D 401/12, A61K 31/415 A61K 31/44	A1	(11) International Publication Number: WO 91/19712 (43) International Publication Date: 26 December 1991 (26.12.91)
(21) International Application Number: PCT/SE91/00416 (22) International Filing Date: 11 June 1991 (11.06.91) (30) Priority data: 9002206-2 20 June 1990 (20.06.90) SE 9002207-0 20 June 1990 (20.06.90) SE (71) Applicant: AKTIEBOLAGET ASTRA [SE/SE]; S-151 85 Södertälje (SE). (72) Inventors: BRÄNDSTRÖM, Arne, Elof ; Anders Mattssonsgatan 13 B, S-425 06 Göteborg (SE). LINDBERG, Per, Lennart ; Knapehall 64, S-436 39 Askim (SE). SUNDÉN, Gunnel, Elisabeth ; Frigångsgatan 10, S-413 01 Göteborg (SE).		(74) Agents: DANIELSSON, Sten et al.; AB Astra, Patent Department, S-151 85 Södertälje (SE). (81) Designated States: AT, AT (European patent), AU, BB, BE (European patent), BF (OAPI patent), BG, BJ (OAPI patent), BR, CA, CF (OAPI patent), CG (OAPI patent), CH, CH (European patent), CI (OAPI patent), CM (OAPI patent), DE, DE (European patent), DK, DK (European patent), ES, ES (European patent), FI, FR (European patent), GA (OAPI patent), GB, GB (European patent), GN (OAPI patent), GR (European patent), HU, IT (European patent), JP, KP, KR, LK, LU, LU (European patent), MC, MG, ML (OAPI patent), MR (OAPI patent), MW, NL, NL (European patent), NO, PL, RO, SD, SE, SE (European patent), SN (OAPI patent), SU, TD (OAPI patent), TG (OAPI patent). Published With international search report.

(54) Title: DIALKOXY-PYRIDINYL-BENZIMIDAZOLE DERIVATIVES, PROCESS FOR THEIR PREPARATION AND THEIR PHARMACEUTICAL USE



(57) Abstract

The novel compounds of formula (I) and physiologically acceptable salts thereof, wherein R¹ and R², which are different, is each H, alkyl containing 1-4 carbon atoms or -C(O)-R⁵; wherein R⁵ is alkyl containing 1-4 carbon atoms or alkoxy containing 1-4 carbon atoms and one of R¹, or R² is always selected from the group -C(O)-R⁵; R³ and R⁴ are the same or different and selected from -CH₃, -C₂H₅, (a), (b), and -CH₂CH₂OCH₃; or R³ and R⁴ together with the adjacent oxygen atoms attached to the pyridine ring and the carbon atoms in the pyridine ring form a ring, wherein the part constituted by R³ and R⁴ is -CH₂CH₂CH₂-, or -CH₂-CH₂- or -CH₂-; as well as intermediates, pharmaceutical compositions containing such compounds as active ingredient and use of the compounds in medicine.

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**Dialkoxy-pyridinyl-benzimidazole derivatives, process for
their preparation and their pharmaceutical use**

5

DESCRIPTION

Field of the invention

10 The object of the present invention is to provide novel
compounds, and therapeutically acceptable salts thereof,
which inhibit exogenously or endogenously stimulated
gastric acid secretion and thus can be used in the
prevention and treatment of peptic ulcer.

15

The present invention also relates to the use of the
compounds of the invention, and therapeutically acceptable
salts thereof, for inhibiting gastric acid secretion in
mammals including man. In a more general sense, the
20 compounds of the invention may be used for prevention and
treatment of gastrointestinal inflammatory diseases, and
gastric acid-related diseases in mammals including man,
such as gastritis, gastric ulcer, duodenal ulcer, reflux
esophagitis, and Zollinger-Ellison syndrome. Furthermore,
25 the compound may be used for treatment of other
gastrointestinal disorders where gastric antisecretory
effect is desirable e.g. in patients with gastrinomas, and
in patients with acute upper gastrointestinal bleeding.
They may also be used in patients in intensive care
30 situations, and pre- and postoperatively to prevent acid
aspiration and stress ulceration. The compounds of the
invention may also be used for treatment or prophylaxis of
inflammatory conditions in mammals, including man,
especially those involving lysozymal enzymes. Conditions
35 that may be specifically mentioned are rheumatoid arthritis
and gout. The compounds may also be useful in the treatment
of diseases related to bone metabolism disorders as well as

the treatment of glaucoma. The invention also relates to pharmaceutical compositions containing the compounds of the invention, or a therapeutically acceptable salt thereof, as active ingredient. In a further aspect, the invention
5 relates to processes for preparation of such new compounds, to novel intermediates in the preparation of the compounds of the invention, and to the use of the active compounds for the preparation of pharmaceutical compositions for the medical use indicated above.

10

It is a specific primary object of the invention to provide compounds with a high level of bioavailability. The compounds of the invention will also exhibit high stability properties at neutral pH and a good potency in regard to
15 inhibition of gastric acid secretion. In addition the compounds of the invention will not block the uptake of iodine into the thyroid gland. It has earlier been disclosed in several lectures from the company, where the inventors are working that thyroid toxicity depends on if the
20 compounds are lipophilic or not. The inventors have now unexpectedly found that it is not the lipophilicity that is the critical parameter. The claimed compounds, which include rather hydrophilic compounds, do not give any thyroid toxic effect and have at the same time high acid
25 secretion inhibitory effect, good bioavailability and stability.

Prior art and background of the invention

- 30 Benzimidazole derivatives intended for inhibiting gastric acid secretion are disclosed in numerous patent documents. Among these can be mentioned GB 1 500 043, GB 1 525 958, US 4 182 766, US 4 255 431, US 4 599 347, EP 124 495, BE 898 880, EP 208 452 and Derwent abstract 87-294449/42.
- 35 Benzimidazole derivatives proposed for use in the treatment or prevention of special gastrointestinal inflammatory diseases are disclosed in US 4 359 465.

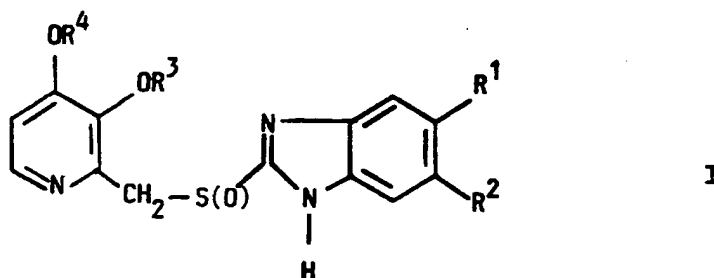
The invention

It has been found that the compounds of the following formula I show high bioavailability. The compounds of the formula I also are effective as inhibitors of gastric acid secretion in mammals and man and do not block the uptake of iodine into the thyroid gland. The compounds of the invention exhibit a high chemical stability in solution at neutral pH.

10

The compounds of the invention are of the following formula I:

15



20 and physiologically acceptable salts thereof

wherein R^1 and R^2 , which are different, is each H, alkyl containing 1-4 carbon atoms or $-C(O)-R^5$; wherein one of R^1 or R^2 is always selected from the group $-C(O)-R^5$; and
 25 wherein R^5 is alkyl containing 1-4 carbon atoms or alkoxy containing 1-4 carbon atoms;

R^3 and R^4 are the same or different and selected from

30 $-CH_3$, $-C_2H_5$, $-CH_2-$ (cyclopropyl), $-CH_2-$ (tetrahydropyran-2-yl) and $-CH_2CH_2OCH_3$ or R^3

and R^4 together with the adjacent oxygen atoms attached to the pyridine ring and the carbon atoms in the pyridine ring form a ring, wherein the part constituted by R^3 and R^4 is

35 $-CH_2CH_2CH_2-$, $-CH_2CH_2-$ or $-CH_2-$.

It should be understood that the expressions "alkyl" and "alkoxy" include straight and branched structures.

The compounds of the invention of the formula I have an asymmetric centre in the sulfur atom, i.e. exist as two optical isomers (enantiomers), or if they also contain one or more asymmetric carbon atoms the compounds have two or more diastereomeric forms, each existing in two enantiomeric forms.

10

Both the pure enantiomers, racemic mixtures (50% of each enantiomer) and unequal mixtures of the two are within the scope of the present invention. It should be understood that all the diastereomeric forms possible (pure enantiomers or racemic mixtures) are within the scope of the invention.

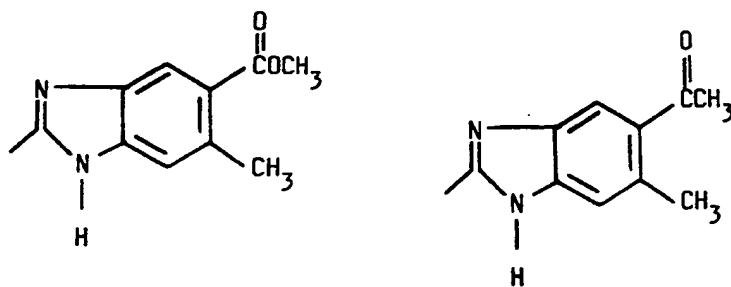
Preferred groups of compounds of the formula I are:

1. Compounds, wherein R^1 and R^2 are selected from H methyl or $-C(O)R^5$, wherein R^5 is alkyl containing 1-4 carbon atoms or alkoxy containing 1-4 carbon atoms.

20

2. Especially preferred benzimidazole structures are

25



30

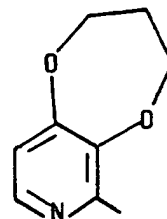
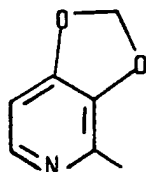
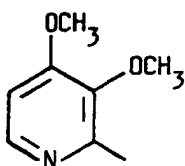
3. Compounds wherein R^3 and R^4 are CH_3 .

4. Compounds wherein R^3 and R^4 together with the adjacent oxygen atoms attached to the pyridine ring and the carbon atoms in the pyridine ring form a ring wherein the part constituted by R^3 and R^4 is $-CH_2CH_2CH_2-$, $-CH_2CH_2-$ or $-CH_2-$.

35

5. Especially preferred pyridine structures are

5



10

6. Further especially preferred specific compounds of the invention are as listed in the following tabulation.

15

R^1	R^2	R^3	R^4
$C(O)OCH_3$	CH_3	CH_3	CH_3
$C(O)CH_3$	CH_3	CH_3	CH_3
20 $C(O)OCH_3$	CH_3		
$C(O)CH_3$	CH_3		
		$-CH_2-$	
		$-CH_2CH_2CH_2-$	

Preparation

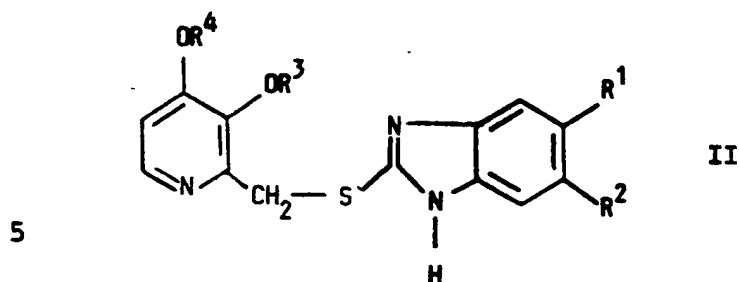
25 The compounds of the invention may be prepared according to the following method:

Oxidizing a compound of the formula II

30

35

6



wherein R^1 , R^2 , R^3 and R^4 are as defined under formula I.

- 10 This oxidation may be carried out by using an oxidizing agent such as nitric acid, hydrogen peroxide, (optionally in the presence of vanadium compounds), peracids, peresters, ozone, dinitrogen tetraoxide, iodosobenzene, N-halosuccinimide, 1-chlorobenzotriazole, t-butylhypochlorite,
- 15 diazabicyclo-[2,2,2]-octane bromine complex, sodium metaperiodate, selenium dioxide, manganese dioxide, chromic acid, ceric ammonium nitrate, bromine, chlorine, and sulfur chloride. The oxidation usually takes place in a solvent such as halogenated hydrocarbons, alcohols, ethers,
- 20 ketones.

The oxidation may also be carried out enzymatically by using an oxidizing enzyme or microbiotically by using a suitable microorganism.

25

- Depending on the process conditions and the starting materials, the compounds of the invention are obtained either in neutral or salt form. Both the neutral compounds and the salts of these are included within the scope of the
- 30 invention. Thus, basic, neutral or mixed salts may be obtained as well as hemi, mono, sesqui or polyhydrates.

- Alkaline salts of the compounds, of the invention are exemplified by their salts with Li^+ , Na^+ , K^+ , Mg^{2+} , Ca^{2+} , and $N^+(R)_4$, where R is (1-4 C)alkyl. Particularly preferred are the Na^+ , Ca^{2+} and Mg^{2+} salts. Especially preferred are the Na^+ and Mg^{2+} salts. Such salts may be prepared by
- 35

reacting a compound with a base capable of releasing the desired cation.

Examples of bases capable of releasing such cations, and
5 examples of reaction conditions are given below.

a) Salts wherein the cation is Li^+ , Na^+ or K^+ are prepared by treating a compound of the invention with LiOH , NaOH or KOH in an aqueous or nonaqueous medium or with LiOR , LiNH_2 ,
10 LiNR_2 , NaOR , NaNH_2 , NaNR_2 , KOR , KNH_2 or KNR_2 , wherein R is an alkyl group containing 1-4 carbon atoms, in a nonaqueous medium.

b) Salts wherein the cation is Mg^{2+} or Ca^{2+} , are prepared by
15 treating a compound of the invention with Mg(OR)_2 , Ca(OR)_2 or CaH_2 ; wherein R is an alkyl group containing 1-4 carbon atoms, in a nonaqueous solvent such as an alcohol (only for the alcoholates), e.g. ROH , or in an ether such as tetrahydrofuran.

20 Racemates obtained can be separated into the pure enantiomers. This may be done according to known methods, e.g. from racemic diastereomeric salts by means of chromatography or fractional crystallization.

25 The starting materials described in the intermediate examples may be obtained according to processes known per se.

30 For clinical use a compound of the invention is formulated into pharmaceutical formulations for oral, rectal, parenteral or other modes of administration. The pharmaceutical formulation contains a compound of the invention normally in combination with a pharmaceutically
35 acceptable carrier. The carrier may be in the form of a solid, semi-solid or liquid diluent, or a capsule. These pharmaceutical preparations are a further object of the

invention. Usually the amount of active compound is between 0.1-95% by weight of the preparation, between 0.2-20% by weight in preparations for parenteral use and between 1-50% by weight in preparations for oral administration.

5

In the preparation of pharmaceutical formulations containing a compound of the present invention in the form of dosage units for oral administration a compound selected may be mixed with a solid, powdered carrier, such as
10 lactose, saccharose, sorbitol, mannitol, starch, amylopectin, cellulose derivatives, gelatin, or another suitable carrier, stabilizing substances such as alkaline compounds e.g. carbonates, hydroxides and oxides of sodium, potassium, calcium, magnesium and the like as well as with
15 lubricating agents such as magnesium stearate, calcium stearate, sodium stearyl fumarate and polyethylenglycol waxes. The mixture is then processed into granules or pressed into tablets. Granules and tablets may be coated with an enteric coating which protects the active compound
20 from acid catalyzed degradation as long as the dosage form remains in the stomach. The enteric coating is chosen among pharmaceutically acceptable enteric-coating materials e.g. beeswax, shellac or anionic film-forming polymers such as cellulose acetate phthalate, hydroxypropyl-methylcellulose
25 phthalate, partly methyl esterified methacrylic acid polymers and the like, if preferred in combination with a suitable plasticizer. To the coating various dyes may be added in order to distinguish among tablets or granules with different active compounds or with different amounts
30 of the active compound present.

Soft gelatine capsules may be prepared with capsules containing a mixture of an active compound of the invention, vegetable oil, fat, or other suitable vehicle
35 for soft gelatine capsules. Soft gelatine capsules may also be enteric-coated as described above. Hard gelatine capsules may contain granules or enteric-coated granules of

an active compound. Hard gelatine capsules may also contain an active compound in combination with a solid powdered carrier such as lactose, saccharose, sorbitol, mannitol, potato starch, amylopectin, cellulose derivatives or
5 gelatine. The hard gelatine capsules may be enteric-coated as described above.

Dosage units for rectal administration may be prepared in the form of suppositories which contain an active substance
10 mixed with a neutral fat base, or they may be prepared in the form of a gelatine rectal capsule which contains an active substance in a mixture with a vegetable oil, paraffin oil or other suitable vehicle for gelatine rectal capsules, or they may be prepared in the form of a ready-made micro
15 enema, or they may be prepared in the form of a dry micro enema formulation to be reconstituted in a suitable solvent just prior to administration.

Liquid preparation for oral administration may be prepared
20 in the form of syrups or suspensions, e.g. solutions or suspensions containing from 0.2% to 20% by weight of the active ingredient and the remainder consisting of sugar or sugar alcohols and a mixture of ethanol, water, glycerol, propylene glycol and/or polyethylene glycol. If desired,
25 such liquid preparations may contain colouring agents, flavouring agents, saccharine and carboxymethyl cellulose or other thickening agents. Liquid preparations for oral administration may also be prepared in the form of a dry powder to be reconstituted with a suitable solvent prior to
30 use.

Solutions for parenteral administration may be prepared as a solution of a compound of the invention in a pharmaceutically acceptable solvent, preferably in a
35 concentration from 0.1% to 10% by weight. These solutions may also contain stabilizing agents and/or buffering agents and may be manufactured in different unit dose ampoules or

vials. Solutions for parenteral administration may also be prepared as a dry preparation to be reconstituted with a suitable solvent extemporaneously before use.

- 5 The typical daily dose of the active substance will depend on various factors such as for example the individual requirement of each patient, the route of administration and the disease. In general, oral and parenteral dosages will be in the range of 5 to 500 mg per day of active substance.

10

The invention is illustrated by the following examples.

Example 1

- 15 Preparation of 5-carbomethoxy-6-methyl-2-[[[(4-cyclopropylmethoxy-3-methoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole.

- 5-Carbomethoxy-6-methyl-2-[[[(4-cyclopropylmethoxy-3-methoxy-2-pyridinyl)methyl]thio]]-1H-benzimidazole (0.42 g, 1.0 mmol) was dissolved in methylene chloride (30 ml). NaHCO₃ (0.17 g, 2.0 mmol) dissolved in water (5 ml) was added and the mixture was cooled to +2°C m-chloroperbenzoic acid, 71% (0.19, 0.80 mmol) dissolved in methylene chloride (5 ml) was added dropwise with stirring. Stirring was continued at +2°C for 15 min. After separation the organic layer was washed with water, dried with Na₂SO₄ and evaporated. To the oily residue acetonitrile (1 ml) was added and after cooling the desired product was filtered off as white crystals (0.15 g, 44%).

30

NMR data are given below.

- 35 Example 2

Preparation of 5-acetyl-6-methyl-2-[[[3,4-ethylenedioxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole.

5-Acetyl-6-methyl-2-[[[3,4-ethylenedioxy-2-pyridinyl)methyl]thio]-1H-benzimidazole (0.17 g, 0.49 mmol) was dissolved in methylene chloride (5 ml). NaHCO_3 (0.082 g, 0.97 mmol) dissolved in water (2 ml) was added and the mixture was cooled to $+2^\circ\text{C}$. m-Chloroperbenzoic acid, 69.5% (0.11 g, 0.44 mmol) dissolved in methylene chloride (2 ml) was added dropwise with stirring.

Stirring was continued at $+2^\circ\text{C}$ for 15 min. After separation the organic layer was extracted with an aqueous 0.20 M NaOH solution (3x2.5 ml, 1.5 mmol). Methyl formate (0.093 ml, 1.5 mmol) was added to the combined aqueous solutions and after 15 minutes the solution was extracted with methylene chloride. The organic solution was dried over Na_2SO_4 and evaporated leaving a white crystalline product which was washed with ether. In this way the desired compound was obtained (0.050 g, 30%).

NMR data are given below.

Example 3

Preparation of 5-carbomethoxy-6-methyl-2-[[[3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole

5-Carbomethoxy-6-methyl-2-[[[3,4-dimethoxy-2-pyridinyl)methyl]thio]-1H-benzimidazole (1.03 g, 0.00276 mol) was dissolved in CH_2Cl_2 (30 ml). NaHCO_3 (0.46 g, 0.0055 mol) in H_2O (10 ml) was added and the mixture was cooled to $+2^\circ\text{C}$. m-chloroperbenzoic acid 69.5% (0.62 g, 0.0025 mol) dissolved in CH_2Cl_2 (5 ml) was added dropwise under stirring. Stirring was continued at $+2^\circ\text{C}$ for 15 min. After separation the organic layer was extracted with an aqueous 0.2 M NaOH solution (3x15 ml, 0.009 mol). After

separation the aqueous solutions were combined and neutralized with methyl formate (0.56 ml, 0.009 mol) in the presence of CH_2Cl_2 (25 ml). After separation the organic layer was dried over Na_2SO_4 and evaporated under reduced pressure. The residue was crystallized from CH_3CN (10 ml) giving the title compound (0.68 g, 70 %).

NMR data are given below.

10 Example 4

Preparation of 5-acetyl-6-methyl-2-[[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole

15 5-Acetyl-6-methyl-2-[[[(3,4-dimethoxy-2-pyridinyl)methyl]thio]-1H-benzimidazole (3.75 g, 10 mmol) was dissolved in CH_2Cl_2 (70 ml). NaHCO_3 (1.76 g, 21 mmol) in H_2O (25 ml) was added and the mixture was cooled to $+3^\circ\text{C}$. m-Chloroperbenzoic acid 69.5% (2.43 g, 9.8 mmol) dissolved in CH_2Cl_2 (20 ml) was added dropwise under stirring. Stirring was continued for 10 min. The phases were separated and the organic phase was dried over Na_2SO_4 and evaporated under reduced pressure. The residue was crystallized from CH_3CN giving the title compound (2.25 g, 60%).

25

NMR data are given below.

Example 5

30 **Preparation of 5-carbethoxy-2-[[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole**

5-Carbethoxy-2-[[[(3,4-dimethoxy-2-pyridinyl)methyl]thio]-1H-benzimidazole (95.2% pure) (1.4 g, 0.0036 mol) was dissolved in CH_2Cl_2 (30 ml). NaHCO_3 (0.6 g, 0.0072 mol) in H_2O (10 ml) was added and the mixture was cooled to $+2^\circ\text{C}$. m-Chloroperbenzoic acid 69.5 % (0.87 g, 0.0035 mol)

dissolved in CH_2Cl_2 (5 ml) was added dropwise under stirring. Stirring was continued at $+2^\circ\text{C}$ for 10 min. The phases were separated and the organic phase was dried over Na_2SO_4 and evaporated under reduced pressure. The residue
5 was crystallized from CH_3CN (15 ml) giving the title compound (0.76 g, 54 %).

NMR data are given below.

10 Example 6

Preparation of 5-acetyl-6-methyl-2-[[[(3,4-propylenedioxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole.

15 The compound was prepared from 5-acetyl-6-methyl-2-[[[(3,4-propylenedioxy-2-pyridinyl)methyl]thio]-1H-benzimidazole and m-chloroperbenzoic acid on a 0.01 mmol scale according to standard procedures.

20 NMR data are given below.

Example 7

5-Acetyl-6-methyl-2-[[[(3,4-methylenedioxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole.
25

5-Acetyl-6-methyl-2-[[[(3,4-methylenedioxy-2-pyridinyl)methyl]thio]-1H-benzimidazole (140 mg, 0.41 mmol) was dissolved in methylene chloride (20 ml) and sodium
30 hydrogen carbonate (5 ml, 1M). The mixture was stirred at ambient temperature and MCPBA (100 mg, 0.41 mmol, 70%) dissolved in methylene chloride (10 ml) was added portionwise. After 10 min sodium thiosulphate (100 mg) was added whereupon the phases were separated. The organic phase
35 was dried over sodium sulphate, filtered and concentrated under reduced pressure. The residue was chromatographed on

silica ($\text{CH}_2\text{Cl}_2/\text{MeOH}/\text{NH}_3$, 97.5:2.5:sat.) Yield: 90 mg (61%) of the title compound. Mp: 178-180°C (dec., uncorr.).

NMR data are given below.

5

Example 8

Preparation of 5-acetyl-6-methyl-2-[[[(3-methoxy-4-(5-methyl-1,3-dioxan-5-yl-methoxy)-2-pyridinyl)methyl]-sulfinyl]-1H-benzimidazole

A stirred mixture of 5-acetyl-6-methyl-2-[[[(3-methoxy-4-(5-methyl-1,3-dioxan-5-yl-methoxy)-2-pyridinyl)methyl]thio]-1H-benzimidazole (87 mg, 0.19 mmol) in 20 ml CH_2Cl_2 and NaHCO_3 (32 mg, 0.38 mmol) in 5 ml H_2O was cooled to 0°C and treated with 3-chloro-perbenzoic acid (47 mg 70%, 0.19 mmol). After reacting for 10 min the layers were separated (the aqueous layer was washed once more with 5 ml CH_2Cl_2) and the organic layer extracted with 10 ml H_2O containing NaOH (15 mg, 38 mmol). The alkaline aqueous layer was collected and treated with several portions of methyl formate (each 23 μl , 38 mmol) until the solution turned opaque. The aqueous layer was extracted with 25 + 10 ml CH_2Cl_2 . The two latter organic layers were combined, dried over MgSO_4 and evaporated. The residue was chromatographed (SiO_2 , $\text{CH}_2\text{Cl}_2/\text{MeOH}$ saturated with $\text{NH}_3(\text{g})$, 93/7) yielding 40 mg (44%) pure sulfoxide.

NMR data are given below.

30 Example 9

Preparation of 5-acetyl-6-methyl-2-[[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole, sodium salt

35 5-Acetyl-6-methyl-2-[[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole (0.50 g, 1.3 mmol) dissolved in dichloromethane and sodium hydroxide (51

mg, 1.3 mmol) dissolved in water (6 ml) were transferred to a separatory funnel. The mixture was shaken to equilibrium whereupon the solvent phases were separated. The aqueous solution was washed with dichloromethane and then freeze
5 dried.

NMR data are given below.

Example 10

10

Preparation of 5-acetyl-6-methyl-2-[[[(4-cyclopropylmethoxy-3-methoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole

5-Acetyl-6-methyl-2-[[[(4-cyclopropylmethoxy-3-methoxy-2-pyridinyl)methyl]thio]-1H-benzimidazole (40 mg, 0.10 mmol)
15 was dissolved in methylene chloride (10 ml) and sodium hydrogen carbonate (3 ml, 1M). The mixture was stirred at ambient temperature and MCPBA (25 mg, 0.10 mmol, 70 %) dissolved in methylene chloride (5 ml) was added
20 portionwise. After 10 min sodium thiosulphate (30 mg) was added whereupon the phases were separated. The organic phase was dried over sodium sulphate, filtered and concentrated under reduced pressure. The residue was chromatographed on silica (CH₂Cl₂/MeOH/NH₃, 97.5:2.5:sat.) Yield 30 mg (73 %)
25 of the title compound.

Table 1

Ex	Solvent	NMR data δ ppm
30		
1	CDCl ₃ (300 MHz)	0.30-0.35 (m, 2H), 0.60-0.67 (m, 2H), 1.2-1.3 (m, 1H) 2.67 (s, 3H), 3.83 (d, 2H), 3.86 (s, 3H), 3.90 (s, 3H), 4.72 (d, 1H), 4.86 (d, 1H), 6.71 (d, 1H), 7.35 (b, 1H), 8.09 (d, 1H), 8.24 (b, 1H),
35		

2	CDCl ₃ (500 MHz)	2.65 (s, 3H), 2.66 (s, 3H), 3.9-4.2 (m, 4H), 4.70 (d, 1H), 4.82 (d, 1H), 6.75 (d, 1H), 7.3 (b, 1H), 7.92 (d, 1H), 8.2 (b, 1H),
5		
3	CDCl ₃ (500 MHz)	2.70 (s, 3H), 3.85 (s, 3H), 3.90 (s, 3H), 3.95 (s, 3H), 4.70 (d, 1H), 4.90 (d, 1H), 6.8 (d, 1H), 7.30 (b, 1H), 8.20 (d, 1H), 8.35 (b, 1H).
10		
4	CDCl ₃ (300 MHz)	2.60 (s, 6H), 3.85 (s, 3H), 3.85 (s, 3H), 4.70 (d, 1H), 4.90 (d, 1H), 6.80 (d, 1H), 7.30 (b, 1H), 8.15 (d, 1H), 8.20 (b, 1H)
15		
5	CDCl ₃ (300 MHz)	1.45 (t, 3H), 3.85 (s, 3H), 3.90 (s, 3H), 4.40 (q, 2H), 4.65 (d, 1H), 4.40 (d, 1H), 6.80 (d, 1H), 7.50 7.80 (b, 1H) 8.05 (d, 1H), 8.20 (d, 1H), 8.25, 8.55 (b, 1H)
20		
25		
6	CDCl ₃ (500 MHz)	2.16 (m, 2H), 2.64 (s, 3H), 2.66 (s, 3H), 4.23 (t, 2H), 4.30 (t, 2H), 4.68 (d, 1H), 4.88 (d, 1H), 6.83 (d, 1H), 7.3-7.5 (b, 1H), 8.01 (d, 1H), 8.1-8.2 (b, 1H).
30		
7	CDCl ₃ (300 MHz)	2.66 (s, 6H), 4.54 (d, 1H), 4.75 (d, 1H), 5.80 (s, 1H), 5.87 (s, 1H), 6.77 (d, 1H), 7.93 (br. 1H), 8.07 (d, 1H), 8.12 (br. 1H)
35		

17

8	CDCl ₃ (300 MHz)	0.91 (s, 3H), 2.63 (s, 3H), 2.64 (s, 3H), 3.49 (d, 2H), 3.84 (s, 3H), 3.94 (d, 2H), 4.15 (m, 2H), 4.66 (d, 1H), 4.73 (d, 1H), 4.86 (d, 1H), 5.02 (d, 1H), 6.89 (d, 1H), 7.33 (s, 1H), 8.08 (s, 1H), 8.14 (d, 1H)
5		
9	D ₂ O (protons in water were set to 4.82 ppm) (300 MHz)	2.66 (s, 3H), 2.81 (s, 3H), 3.81 (s, 3H), 4.02 (s, 3H), 4.73 (d, 1H), 4.91 (d, 1H), 7.16 (d, 1H), 7.62 (s, 1H), 8.23 (d, 1H), 8.30 (s, 1H)
10		
15	CDCl ₃ (300 MHz)	0.33 (m, 2H), 0.65 (m, 2H), 1.24 (m, 1H), 2.63 (s, 3H), 2.64 (s, 3H), 3.84 (d, 2H), 3.88 (s, 3H), 4.73 (d, 1H), 4.83 (d, 1H), 6.73 (d, 1H), 7.35 (s, 1H), 8.08 (s, 1H), 8.11 (d, 1H)
20		

Example of intermediates25 Example I 1

Preparation of 5-carbomethoxy-6-methyl-2-[[[(4-cyclopropylmethoxy-3-methoxy-2-pyridinyl)methyl]thio]-1H-benzimidazole.

30

To a solution of 5-carbomethoxy-6-methyl-2-mercapto-1H-benzimidazole (0.58 g, 2.6 mmol) in methanol (25 ml) aqueous NaOH (1.0 ml 5M, 5.0 mmol) and 4-cyclopropylmethoxy-3-methoxy-2-chloromethyl pyridine hydrochloride (prepared according to processes known per se.) (0.63 g, 2.4 mmol) dissolved in methanol (25 ml) were added in the given order. The mixture was refluxed for one hour whereupon the solution

was evaporated. The residue was partitioned between methylene chloride and water. After separation the organic solution was dried over Na_2SO_4 and evaporated giving a yellow syrup (1.0 g, 100%).

5

NMR data are given below.

Example I 2

10 5-Acetyl-6-methyl-2-[[[(3,4-ethylenedioxy-2-pyridinyl)methyl]thio]-1H-benzimidazole

To a solution of 5-acetyl-6-methyl-2-mercapto-1H-benzimidazole (0.14 g, 0.66 mmol) in methanol (2 ml) aqueous NaOH (0.25 ml 5M, 1.25 mmol) and 3,4-ethylenedioxy-2-chloromethyl pyridine hydrochloride (0.13 g, 0.60 mmol) dissolved in methanol (2 ml) were added in the given order. The mixture was refluxed for one hour whereupon the solution
20 was evaporated. The residue was partitioned between methylene chloride and water. After separation the organic solution was dried over Na_2SO_4 and evaporated giving a yellow syrup (0.17 g, 81%).

25 NMR data are given below.

Example I 3

30 Preparation of 5-carbomethoxy-6-methyl-2-[[[(3,4-dimethoxy-2-pyridinyl)methyl]thio]-1H-benzimidazole

5-Carbomethoxy-6-methyl-2-mercapto-1H-benzimidazole (0.67 g, 0.003 mol) and NaOH (0.12 g, 0.003 mol) in H_2O (0.6 ml) were dissolved in CH_3OH (15 ml). 3,4-dimethoxy-2-chloromethylpyridine hydrochloride, (≈ 0.0036 mol) as a crude material in CH_3OH (10 ml) and NaOH (0.144 g, 0.0036 mol) in H_2O (0.72 ml) were added. The mixture was heated to reflux

and the reflux was continued for 1 hour. CH_3OH was evaporated off and the crude material was purified by chromatography on a silica column using $\text{CH}_2\text{Cl}_2\text{-CH}_3\text{OH}$ (98-2) as eluent, giving (1.03 g, 92%) of the pure title compound.

5 NMR data are given below.

Example I 4

Preparation of 5-acetyl-6-methyl-2-[[[3,4-dimethoxy-2-pyridinyl)methyl]thio]-1H-benzimidazole

5-Acetyl-6-methyl-2-mercapto-1H-benzimidazole (4.2 g, 20 mmol) and NaOH (0.8 g, 20 mmol) in H_2O (1 ml) were dissolved in 60 ml ethanol. 3,4-dimethoxy-2-chloromethylpyridine hydrochloride (≈ 17 mmol) as a crude material was added and the mixture was heated to boiling. NaOH (0.7 g, 17 mmol) in H_2O (1 ml) was added and the reflux was continued for 6 hours. The solvent was evaporated off and the residue was diluted with methylene chloride and water. The organic phase was dried over Na_2SO_4 and the solvent was removed under reduced pressure. Crystallizing from acetonitrile gave the title compound, (3.75 g, 62%).

NMR data are given below.

25 Example I 5

Preparation of 5-carbethoxy-2-[[[3,4-dimethoxy-2-pyridinyl)methyl]thio]-1H-benzimidazole

5-Carbethoxy-2-mercapto-1H-benzimidazole (2.0 g, 9 mmol) and NaOH (0.36 g, 9 mmol) in H_2O (1 ml) were dissolved in ethanol (30 ml). 3,4-dimethoxy-2-chloromethylpyridine hydrochloride (≈ 6.6 mmol) as a crude material were added and the mixture was heated to boiling. NaOH (0.26 g, 6.6 mmol) in H_2O (1 ml) was added and the reflux was continued for 6 hours. The solvent was evaporated off and the residue was diluted with methylene chloride and water. The organic phase

was dried over Na_2SO_4 and the solvent removed under reduced pressure. Crystallizing from CH_3CN gave the desired product (1.75 g, 71%).

NMR data are given below.

5

Example I 6

Preparation of 5-acetyl-6-methyl-2-[[[3,4-propylenedioxy-2-pyridinyl)methyl]thio]-1H-benzimidazole

10

The compound was prepared from 5-acetyl-2-mercapto-6-methyl-1H-benzimidazole and 2-chloromethyl-3,4-propylenedioxy-pyridine on a 0.01 mmol scale according to standard procedures.

15 NMR data are given below.

Example I 7

Preparation of 5-acetyl-6-methyl-2-[[[3,4-methylenedioxy-2-pyridinyl)methyl]thio]-1H-benzimidazole

20

2-Chloromethyl-3,4-methylenedioxy-pyridine (90 mg, 0.52 mmol) and 5-acetyl-6-methyl-2-mercaptobenzimidazole (214 mg, 1.04 mmol) were dissolved in ethanol (15 ml). The pH value of the solution was adjusted to 9 (0.2M NaOH) whereupon the solution was refluxed for 10 min. After concentration of the reaction mixture at reduced pressure the residue was taken up in methylene chloride (10 ml) and brine (2 ml). The phases were separated and the organic phase was dried over sodium sulphate, filtered and concentrated at reduced pressure. The residue was chromatographed on silica (ethyl acetate). Yield: 140 mg (79%) of the title compound. Mp: 141-143°C (uncorr.)

30

NMR data are given below.

35

Example I 8

**Preparation of 5-acetyl-6-methyl-2-[[[3-methoxy-4-(5-methyl-1,3-dioxan-5-yl-methoxy)-2-pyridinyl)methyl]-thio]-1H-
5 benzimidazole**

A solution of 2-(hydroxymethyl)-3-methoxy-4-(5-methyl-1,3-dioxan-5-yl-methoxy)pyridine (0.34 g, 1.3 mmol) in 10 ml CH_2Cl_2 was cooled to 0°C and treated with SOCl_2 (0.12 ml, 1.7 mmol). The solution was allowed to warm to room temperature and reacted for 1 h. Evaporation of the solvent furnished a quantitative yield of the corresponding chloromethyl derivative as the hydrochloride. DI-MS, m/z (%): 289 and 287 (11 and 38). A suspension of 5-acetyl-2-mercapto-6-methyl-1H-benzimidazole (0.29 g, 1.4 mmol) in 10 ml MeOH was treated with a solution of NaOH (0.10 g, 2.6 mmol) in 1.5 ml H_2O . The formed solution was treated with the prepared chloromethyl compound and reacted for 21 h at room temperature. The solvent was evaporated and the residue taken up in 20 ml 2.5% NaOH. The aqueous layer was extracted with 50 + 25 ml CH_2Cl_2 , the organic layers combined, dried over MgSO_4 , and evaporated leaving 0.49 g (82%) title compound as a tanned foam. NMR data are given below.

25

Example I 9

Preparation of 5-acetyl-6-methyl-2-[[[4-cyclopropylmethoxy-3-methoxy-2-pyridinyl)methyl]thio]-1H-benzimidazole

30

2-Chloromethyl-4-cyclopropylmethoxy-3-methoxypyridine (50 mg, 0.22 mmol) and 5-acetyl-6-methyl-2-mercaptobenzimidazole (50 mg, 0.24 mmol) were dissolved in ethanol (15 ml). The pH value of the solution was adjusted to 9 (0.2M NaOH) whereupon the solution was refluxed for 10 min. After concentration of the reaction mixture at reduced pressure the residue was taken up in methylene chloride (10 ml) and

35

brine (2 ml). The phases were separated and the organic phase was dried over sodium sulphate, filtered and concentrated at reduced pressure. The residue was chromatographed on silica (ethyl acetate). Yield: 40 mg (46%) of the title compound.
NMR data are given below.

Example I 10

10 Preparation of 4-chloro-3-hydroxyethoxy-2-methylpyridine

A solution of 4-chloro-3-methoxyethoxy-2-methylpyridine (2.78 g, 0.014 mol) in dry CDCl_3 (≈ 14 ml) under Ar was treated with TMSI (5.10 ml, 0.036 mol) for 23 h at room temperature. The reaction mixture was partitioned between 100 ml CH_2Cl_2 and 100 ml 1M HCl. The aqueous layer was collected, washed once more with 50 ml CH_2Cl_2 , and then treated with Na_2CO_3 until the pH was ≈ 10 . The aqueous layer was extracted with 100 + 50 ml CH_2Cl_2 . The two latter organic layers were combined, dried over MgSO_4 and evaporated leaving 2.31 g enriched product.

Chromatography (silica gel, diethyl ether followed by diethyl ether/MeOH;95/5) afforded 1.06 g (40%) pure product.
NMR data are given below.

Example I 11

Preparation of 3,4-ethylenedioxy-2-methylpyridine

A mixture of 4-chloro-3-hydroxyethoxy-2-methylpyridine (1.03g, 0.0055 mol) and NaH (55% in oil, 599 mg, 0.0138 mol) in 600 ml THF was refluxed for 15 h. Excess NaH was destroyed with 3 ml of H_2O . The solvent was evaporated and the residue partitioned between 100 ml 1M HCl and 100 ml CH_2Cl_2 . The aqueous layer was collected, washed once more with 100 ml CH_2Cl_2 and then treated with Na_2CO_3 until the pH

was ≈10. The aqueous layer was extracted with 150 + 100 ml CH_2Cl_2 . The two latter organic layers were combined, dried over MgSO_4 , and evaporated leaving 720 mg enriched product. Chromatography (silica gel, diethyl ether) furnished 0.49 g (59%) pure product. NMR data are given below.

Example I 12

10 Preparation of 3,4-ethylenedioxy-2-hydroxymethyl-pyridine

The title compound was prepared on a 3.2 mmol scale according to standard procedures yielding 395 mg (77%) pure product.

15

NMR data for the intermediate are given below.

Example I 13

20 Preparation of 3-(3-hydroxy-1-propoxy)-2-methyl-4-pyrone

A suspension of 3-hydroxy-2-methyl-4-pyrone (25 g, 200 mmol), 3-bromo-1-propanol (70 g, 500 mmol) and K_2CO_3 (111 g 800 mmol) in 600 ml acetone was stirred for three days. The solvent was evaporated and the residue partitioned between 300 ml methylene chloride and 500 ml 2.5% NaOH. The aqueous layer was separated and extracted with 2x300 ml methylene chloride. The organic phases were combined, dried over Na_2SO_4 and evaporated at 50°C. Eight grams of the residue (24 g) was chromatographed on silica gel with methanol/methylene chloride (5:95) as eluent which afforded 2.7 g (22%) of the desired product as an oil. NMR data are given below.

35 Example I 14

Preparation of 3-(3-methoxy-1-propoxy)-2-methyl-4-pyrone

A mixture of 3-(3-hydroxy-1-propoxy)-2-methyl-4-pyrone (1.4 g, 7.6 mmol), 85% KOH (0.55 g, 8.4 mmol) and methyl iodide (11 g, 76 mmol) was stirred at room temperature for one day.

5 The red solution was partitioned between methylene chloride and half saturated aqueous ammonium chloride solution. The organic phase was washed with water, dried over Na_2SO_4 and evaporated. The residue was purified by chromatography on silica gel with methanol/methylene chloride (3:97) as

10 eluent. Removing the eluent by film evaporation afforded 0.31 g (20%) of the desired product as an oil.

NMR data are given below.

Example I 15

15

Preparation of 3-(3-methoxy-1-propoxy)-2-methyl-4-pyridone

A solution of 3-(3-methoxy-1-propoxy)-2-methyl-4-pyrone (0.31 g, 1.7 mmol) in 50 ml concentrated aqueous NH_3 was

20 heated to 120°C for 2 h in an autoclave. The reaction mixture was transferred to a round bottomed flask and evaporation off the solvent afforded 0.32 g (100%) product as a yellow oil.

NMR data are given below.

25

Example I 16

Preparation of 4-chloro-3-(3-methoxy-1-propoxy)-2-methyl-pyridine

30

A solution of 3-(3-methoxy-1-propoxy)-2-methyl-4-pyridone (0.32 g, 1.6 mmol) in 50 ml POCl_3 was refluxed for 14 h. The POCl_3 was evaporated off and the residue was partitioned between methylene chloride and water. The aqueous layer was

35 separated, treated with K_2CO_3 until pH=10 and extracted with methylene chloride. The organic layer was dried over Na_2SO_4 and evaporated. The residue was purified by chromatography

on silica gel with methanol/methylene chloride (3:97) as eluent. Evaporation off the solvent afforded 0.12 g (34%) product as a red oil.

NMR data are given below.

5

Example I 17

Preparation of 4-chloro-3-(3-hydroxy-1-propoxy)-2-methylpyridine

10

To a solution of 4-chloro-3-(3-methoxy-1-propoxy)-2-methylpyridine (120 mg, 0.56 mmol) in 2 ml of CDCl_3 was added trimethylsilyl iodide (0.16 ml, 1.3 mmol), this was done in a NMR tube. The reaction was complete after four days as indicated by the absence of a signal for the OCH_3 protons at 3.3 ppm in the NMR spectrum. The solution was poured over 10 ml of 1 M HCl whereupon the mixture was stirred for 5 minutes with 10 ml of methylene chloride. The aqueous layer was separated, treated with K_2CO_3 until pH=10 and extracted with methylene chloride. The organic phase was dried over Na_2SO_4 and evaporated. This afforded 0.049 g (43%) of the desired product as a yellow oily film.

20

NMR data are given below.

25

Example I 18

Preparation of 2-methyl-3,4-propylenedioxy-pyridine

A solution of 4-chloro-3-(3-hydroxy-1-propoxy)-2-methylpyridine (49 mg, 0.24 mmol) in 3 ml of DMSO was heated for 2 h at 70°C with 55% NaH (32 mg, 0.73 mmol). The mixture was cooled, diluted with water and extracted with methylene chloride. The organic solution was evaporated and the residue was chromatographed on silica gel with methylene chloride as eluent. The solvent was evaporated which afforded 22 mg (55%) of a yellow oil.

35

NMR data are given below.

Example I 19**Preparation of 2-hydroxymethyl-3,4-propylene-dioxypyridine**

5

The title compound was prepared from 2-methyl-3,4-propylenedioxypyridine on a 0.01 mmol scale according to standard procedures yielding 3 mg (11%) product. NMR data are given below.

10

Example I 20**Preparation of 2-chloromethyl-3,4-propylene-dioxypyridine**

15 The title compound was prepared from 2-hydroxymethyl-3,4-propylenedioxypyridine in a quantitative yield on a 0.01 mmol scale according to standard procedures. The compound was used in the synthesis without purification and characterisation.

20

Example I 21**Preparation of 2-methyl-3,4-methylenedioxypyridine**

25 2-Methyl-3-hydroxy-4-pyridone (1.25 g, 10 mmol) was dissolved in dry DMSO (20 ml). Dibromomethane (3.5 g, 20 mmol) was added followed by sodium hydride (1 g, >20 mmol, 50-60% in oil). The mixture was left at ambient temperature under stirring for 3 days whereupon it was poured into brine
30 (50 ml). The water-DMSO solution was extracted with methylene chloride (3x50 ml) and the collected extracts were used directly in the next step. A sample for NMR analysis was withdrawn.

35 NMR data are given below.

Example I 22**Preparation of 2-methyl-3,4-methylenedioxy pyridine-N-oxide**

- 5 To the methylene chloride solution of 2-methyl-3,4-methylenedioxy pyridine from example I 21 sodium hydrogen carbonate (1M, 50 ml) and MCPBA (4 g, 70%) were added. The mixture was stirred at ambient temperature for 15 min whereupon the excess of MCPBA was destroyed with addition of
- 10 sodium thiosulphate (1 g). The organic phase was separated and the aqueous phase was extracted with methylene chloride (3x50 ml). The collected organic phases were concentrated under reduced pressure and chromatographed on silica ($\text{CH}_2\text{Cl}_2/\text{MeOH}$, 90:10). Yield: 120 mg (7,8%) of the title
- 15 compound.

NMR data are given below.

Example I 23**20 Preparation of 2-hydroxymethyl-3,4-methylenedioxy pyridine**

- 2-Methyl-3,4-methylenedioxy pyridine-N-oxide (120 mg, 0.78 mmol) was dissolved in acetic anhydride (10 ml) and the solution was heated at 110 °C for 15 min, whereupon the
- 25 mixture was concentrated under reduced pressure. The residue was dissolved in methanol (20 ml) and sodium hydroxide (3 drops, 6M) was added. After 30 min at ambient temperature the mixture was neutralised with acetic acid (pH 6) and concentrated under reduced pressure. The residue was
- 30 chromatographed on silica (hexane/ethyl acetate, 1:1). Yield: 90 mg (75%) of the title compound.

NMR data are given below.

35 Example I 24**Preparation of 2-chloromethyl-3,4-methylenedioxy pyridine**

2-Hydroxymethyl-3,4-methylenedioxy pyridine (90 mg, 0.59 mmol) was dissolved in methylene chloride (10 ml) and thionyl chloride (240 mg, 2 mmol) was added. After 10 min at ambient temperature the mixture was hydrolysed with sodium hydrogen carbonate and the phases were separated. The organic phase was dried over sodium sulphate, filtered and concentrated under reduced pressure. Yield: 90 mg (88%) of the title compound (crude).

10

NMR data are given below.

Example I 25

15 Preparation of 3-methoxy-2-methyl-4-(5-methyl-1,3-dioxan-5-yl-methoxy)pyridine-N-oxide

A deareated solution of 5-(hydroxymethyl)-5-methyl-1,3-dioxane (1.19 g, 9 mmol) in 125 ml dry THF was treated with NaH (0.79 g 55% dispersion in oil, 18 mmol) for 20 min. 4-Chloro-3-methoxy-2-methylpyridine-N-oxide (1.04 g, 6 mmol) was added and the mixture was refluxed for 26 h. Excess NaH was quenched with 10 ml of H₂O and the solvent evaporated. The residue was partitioned between 150 ml CH₂Cl₂ and 50 ml 5% Na₂CO₃. The organic layer was passed through a phase separation paper and evaporated leaving 1.83 g enriched product. Chromatography (SiO₂CH₂Cl₂/MeOH, 95/5) afforded 0.39 g (24%) pure title compound as a tanned oil.

30 NMR data are given below.

Example I 26

35 Preparation of 2-(hydroxymethyl)-3-methoxy-4-(5-methyl-1,3-dioxan-5-yl-methoxy)pyridine

A solution of 3-methoxy-2-methyl-4-(5-methyl-1,3-dioxan-5-yl-methoxy)pyridine-N-oxide (0.39 g, 1.5 mmol) in 4.5 ml $(\text{CH}_3\text{CO})_2\text{O}$ was heated to 100°C for 4 h. Excess $(\text{CH}_3\text{CO})_2\text{O}$ was azeotroped off 4 times with 75 ml portions of abs. EtOH leaving 0.42 g (90%) crude 3-methoxy-4-(5-methyl-1,3-dioxan-5-yl-methoxy)-2-pyridinyl)-methyl acetate.

The crude acetate was treated with 20 ml 2M NaOH for 1 h at 100 °C. The aqueous layer was extracted with 75 + 50 + 25 ml CH_2Cl_2 . The organic layers were combined, dried over MgSO_4 , and evaporated leaving 0.34 g (97%) product pure enough for further use.

NMR data are given below.

Table 2

Ex	Solvent	NMR data δ ppm
20		
I 1	CDCl_3 (300 MHz)	0.37-0.42 (m, 2H), 0.67-0.73 (m, 2H), 1.25-1.40 (m, 1H) 2.69 (s, 3H), 3.90 (s, 3H), 3.94 (d, 2H), 3.98 (s, 3H), 4.40 (s, 2H)
25		6.81 (d, 1H), 7.3 (b, 1H), 8.2 (b, 1H), 8.22 (d, 1H),
30		
I 2	CDCl_3 (500 MHz)	2.64 (s, 3H), 2.66 (s, 3H), 4.35 (s, 2H), 4.40 (s, 4H), 6.85 (d, 1H), 7.30 (s, 1H), 8.06 (d, 1H), 8.08 (s, 1H).
35		
I 3	CDCl_3 (300 MHz)	2.70 (s, 3H), 3.90 (s, 3H), 3.95 (s, 3H), 4.00 (s, 3H), 4.40 (s, 2H), 6.90 (d, 1H), 7.35 (s, 1H), 8.20 (s, 1H), 8.25 (d, 1H)

30

5	I 4	CDCl ₃ (300 MHz)	2.60 (s, 3H), 2.65 (s, 3H), 3.90 (s, 3H), 3.90 (s, 3H), 4.35 (s, 2H), 6.85 (d, 1H), 7.25 (s, 0.6H), 7.40 (s, 0.4H), 7.85 (s, 0.4H), 8.05 (s, 0.6H), 8.30 (m, 1H)
10	I 5	CDCl ₃ (300 MHz)	1.40 (m, 3H), 3.90 (s, 3H), 3.90 (s, 3H), 4.40 (m, 4H), 6.90 (dd, 1H), 7.45 (d, 0.4H), 7.60 (d, 0.6H), 7.90 (m, 1H), 8.20 (s, 0.6H), 8.25 (m, 1H), 8.25 (s, 0.4H)
15	I 6	CDCl ₃ (500 MHz)	2.32 (p, 2H), 2.64 (s, 3H), 2.66 (s, 3H), 4.37-4.43 (m, 4H), 4.39 (s, 2H), 6.88-6.90 (m, 1H), 7.29 (s, 0.6H), 7.42 (s, 0.4H), 7.85 (s, 0.4H), 8.07 (s, 0.6H), 8.11 (m, 1H)
20	I 7	CDCl ₃ (300 MHz)	2.648 (s, 3H), 2.652 (s, 3H), 4.32 (s, 2H), 6.14 (s, 2H), 6.85 (d, 1H), 7.34 (br. 1H), 8.00 (br. 1H), 8.20 (d, 1H)
25	I 8	CDCl ₃ (300 MHz)	0.98 (s, 3H), 2.65 (coinciding s, 6H), 3.53 (d, 2H), 3.95 (s, 3H), 4.00 (d, 2H), 4.25 (s, 2H), 4.39 (s, 2H), 4.69 (m, 1H), 5.06 (m, 1H), 6.9-7.0 (2 d, 1H), 7.3-7.5 (several b, 1H), 7.8-8.1 (several b, 1H), 8.2-8.3 (2 d, 1H), 13.2 (b, 1H)
35	I 9	CDCl ₃ (300 MHz)	0.38 (m, 2H), 0.69 (m, 2H), 1.31 (m, 1H), 2.63 (s, 3H), 2.636 (s, 3H), 3.93 (d, 2H), 3.98 (s, 3H),

31

4.40 (s, 2H), 6.81 (d, 1H), 7.33
(s, 1H), 7.98 (s, 1H), 8.22 (d, 1H)

5 I 10 CDCl₃
(500 MHz)

2.57 (s, 3H), 2.70 (t, 1H) 3.99
(dt, 2H), 4.09 (t, 2H), 7.19 (d,
1H), 8.16 (d, 1H)

10 I 11 CDCl₃
(500 MHz)

2.41 (s, 3H), 4.30 (s, 4H),
6.65 (d, 1H), 7.90 (d, 1H),

I 12 CDCl₃
(500 MHz)

4.11 (b, 1H), 4.33 (m, 4H),
4.69 (b, 2H), 6.76 (d, 1H), 7.99
(d, 1H)

15 I 13 CDCl₃
(300 MHz)

1.85 (p, 2H), 2.30 (s, 3H), 3.85
(q, 2H), 4.00 (t, 2H), 4.35 (t,
1H), 6.35 (d, 1H), 7.65 (d, 1H)

20 I 14 CDCl₃
(300 MHz)

2.00 (p, 2H), 2.32 (s, 3H), 3.35
(s, 3H), 3.56 (t, 2H), 4.13 (t,
2H), 6.33 (d, 1H), 7.59 (d, 1H)

25 I 15 CDCl₃
(300 MHz)

1.98 (p, 2H), 2.45 (s, 3H), 3.38
(s, 3H), 3.61 (t, 2H), 4.08 (t,
2H), 6.53 (d, 1H), 7.63 (d, 1H)

30 I 16 CDCl₃
(300 MHz)

2.09 (p, 2H), 2.54 (s, 3H), 3.38
(s, 3H), 3.63 (t, 2H), 4.04 (t,
2H), 7.16 (d, 1H), 8.13 (d, 1H)

I 17 CDCl₃
(500 MHz)

2.10 (p, 2H), 2.56 (s, 3H), 3.96
(t, 2H), 4.10 (t, 2H), 7.18 (d,
1H), 8.15 (d, 1H)

35 I 18 CDCl₃
(300 MHz)

2.25 (p, 2H), 2.45 (s, 3H), 4.28
(t, 2H), 4.34 (t, 2H), 6.70 (d,
1H), 7.96 (d, 1H)

	I 19	CDCl ₃ (500 MHz)	2.27 (p, 2H), 4.30 (t, 2H), 4.37 (t, 2H), 4.71 (d, 2H), 6.80 (d, 2H), 8.05 (d, 1H)
5	I 21	CDCl ₃ (500 MHz)	2.34 (s, 3H), 5.92 (s, 2H), 6.61 (d, 1H), 7.93 (d, 1H)
10	I 22	CDCl ₃ (500 MHz)	2.42 (s, 3H), 6.12 (s, 2H), 6.59 (d, 1H), 7.90 (d, 1H)
	I 23	CDCl ₃ (300 MHz)	4.73 (s, 2H), 6.05 (s, 2H), 6.76 (d, 1H), 8.09 (d, 1H)
15	I 24	CDCl ₃ (300 MHz)	4.65 (s, 2H), 6.10 (s, 2H), 6.78 (d, 1H), 8.13 (d, 1H)
20	I 25	CDCl ₃ (300 MHz)	0.97 (s, 3H), 2.50 (s, 3H), 3.52 (d, 2H), 3.85 (s, 3H), 3.98 (d, 2H), 4.18 (s, 2H), 4.67 (d, 1H), 5.02 (d, 1H), 6.77 (d, 1H), 8.08 (d, 1H)
25	I 26	CDCl ₃ (300 MHz)	0.98 (s, 3H), 3.52 (d, 2H), 3.86 (s, 3H), 4.00 (d, 2H), 4.09 (m, 1H), 4.20 (s, 2H), 4.68 (d, 1H), 4.75 (d, 2H), 5.02 (d, 1H), 6.88 (d, 1H), 8.20 (d, 1H)

30 The best mode of carrying out the invention known at present is to use the compound according to Example 4 or its salt according to Example 9.

Table 3

Examples of compounds included in the formula I
are given in the following table

Ex.	R ¹	R ²	R ³	R ⁴	Yield%	Ident.data
1	C(O)-OCH ₃	CH ₃	CH ₃	CH ₂	44	NMR
2	C(O)CH ₃	CH ₃	-CH ₂ CH ₂ -		30	NMR
3.	C(O)-OCH ₃	CH ₃	CH ₃	CH ₃	70	NMR
4.	C(O)CH ₃	CH ₃	CH ₃	CH ₃	60	NMR
5.	C(O)OCH ₂ CH ₃	H	CH ₃	CH ₃	54	NMR
6.	C(O)CH ₃	CH ₃	-CH ₂ CH ₂ CH ₂ -			NMR
7.	C(O)CH ₃	CH ₃	-CH ₂ -		61	NMR
8.	C(O)CH ₃	CH ₃	CH ₃	CH ₂	44	NMR
9.	C(O)CH ₃	CH ₃	CH ₃	CH ₃	sodium salt	NMR
10.	C(O)CH ₃	CH ₃	CH ₃	CH ₂	73	NMR

Syrup

A syrup containing 1% (weight per volume) of active substance was prepared from the following ingredients:

5	Compound according to Example 4	1.0 g
	Sugar, powder	30.0 g
	Saccharine	0.6 g
	Glycerol	15.0 g
10	Flavouring agent	0.05 g
	Ethanol 96%	5.0 g
	Distilled water q.s. to a final volume of	100 ml

Sugar and saccharine were dissolved in 60 g of warm water.

- 15 After cooling the active compound was added to the sugar solution and glycerol and a solution of flavouring agents dissolved in ethanol were added. The mixture was diluted with water to a final volume of 100 ml.

20 Enteric-coated tablets

An enteric coated tablet containing 50 mg of active compound was prepared from the following ingredients:

I	Compound according to Example 4	500 g
25	as Mg salt	
	Lactose	700 g
	Methyl cellulose	6 g
	Polyvinylpyrrolidone cross-linked	50 g
	Magnesium stearate 15 g Sodium carbonate	6 g
30	Distilled water	q.s.
II	Cellulose acetate phthalate	200 g
	Cetyl alcohol	15 g
	Isopropanol	2000 g
35	Methylene chloride	2000 g

I Compound according to example 1, powder, was mixed with lactose and granulated with a water solution of methyl cellulose and sodium carbonate. The wet mass was forced through a sieve and the granulate dried in an oven. After drying the granulate was mixed with polyvinylpyrrolidone and magnesium stearate. The dry mixture was pressed into tablet cores (10 000 tablets), each tablet containing 50 mg of active substance, in a tableting machine using 7 mm diameter punches.

10

II A solution of cellulose acetate phthalate and cetyl alcohol in isopropanol/methylene chloride was sprayed onto the tablets I in an Accela Cota[®], Manesty coating equipment. A final tablet weight of 110 mg was obtained.

15

Solution for intravenous administration

A parenteral formulation for intravenous use, containing 4 mg of active compound per ml, was prepared from the following ingredients:

20

Compound according to Example 9	4 g
Sterile water to a final volume of	1000 ml

25 The active compound was dissolved in water to a final volume of 1000 ml. The solution was filtered through a 0.22 μ m filter and immediately dispensed into 10 ml sterile ampoules. The ampoules were sealed.

30 Capsules

Capsules containing 30 mg of active compound were prepared from the following ingredients:

35 Compound according to Example 4	300 g
Lactose	700 g
Microcrystalline cellulose	40 g

Hydroxypropyl cellulose low-substituted	62 g
Disodium hydrogen phosphate	2 g
Purified water	q.s.

- 5 The active compound was mixed with the dry ingredients and granulated with a solution of disodium hydrogen phosphate. The wet mass was forced through an extruder and spheronized and dried in a fluidized bed dryer.
- 10 500 g of the pellets above were first coated with a solution of hydroxypropyl methylcellulose, 30 g, in water, 750 g, using a fluidized bed coater. After drying, the pellets were coated with a second coating as given below:

15 Coating solution:

Hydroxypropyl methylcellulose phthalate	70 g
Cetyl alcohol	4 g
Acetone	200 g
20 Ethanol	600 g

The final coated pellets were filled into capsules.

Suppositories

- 25 Suppositories were prepared from the following ingredients using a welding procedure. Each suppository contained 40 mg of active compound.
- 30 Compound according to Example 4 4 g
- Witepsol H-15 180 g

- The active compound was homogenously mixed with Witepsol H-15 at a temperature of 41°C. The molten mass was volume
- 35 filled into pre-fabricated suppository packages to a net weight of 1.84 g. After cooling the packages were heat

sealed. Each suppository contained 40 mg of active compound.

5 Biological Effects

Bioavailability

Bioavailability is assessed by calculating the quotient between the area under plasma concentration (AUC) curve
10 following intraduodenal (id) administration and intravenous (iv) administration from the rat.

Potency for inhibition of acid secretion

15 The potency for inhibition of acid secretion is measured in the dog, intravenously (iv) and in the female rat, intravenously (iv).

Effects on the uptake of iodine into the thyroid gland

20 The effect of a compound within the invention of the formula I on the uptake of iodine into the thyroid gland is measured as an effect on the accumulation of ^{125}I in the thyroid gland.

25 Biological tests

Inhibition of Gastric Acid Secretion in the Conscious Female Rat.

30 Female rats of the Sprague-Dawley strain are used. They are equipped with cannulated fistulae in the stomach (lumen) for collection of gastric secretions. A fourteen days recovery period after surgery is allowed before testing is commenced.

35 Before secretory tests, the animals are deprived of food but not water for 20 h. The stomach is repeatedly washed through

- the gastric cannula, and 6 ml of Ringer-Glucose given s.c. Acid secretion is stimulated with infusion during 3.5 h (1.2 ml/h, s.c.) of pentagastrin and carbachol (20 and 110 nmol/kg h, respectively), during which time gastric
- 5 secretions are collected in 30-min fractions. Test substances or vehicle are given iv at 90 min after starting the stimulation, in a volume of 1 ml/kg. Gastric juice samples are titrated to pH 7.0 with NaOH, 0.1 mol/L, and acid output is calculated as the product of titrant volume
- 10 and concentration. Further calculations are based on group mean responses from 4-7 rats. The acid output during the periods after administration of test substances or vehicle are expressed as fractional responses, setting the acid output in the 30-min period preceding administration to 1.0.
- 15 Percentage inhibition is calculated from the fractional responses elicited by test compound and vehicle. ED_{50} -values are obtained from graphical interpolation on log dose-response curves, or estimated from single-dose experiments assuming a similar slope for all dose-response curves. The
- 20 results are based on gastric acid secretion during the second hour after drug/vehicle administration.

Bioavailability in the Male Rat.

- 25 Male adult rats of the Sprague-Dawley strain were used. One day, prior to the experiments, all rats were prepared by cannulation of the left carotid artery under anaesthesia. The rats used for the intravenous experiments, were also cannulated in the jugular vein. (Ref. V Popovic and P
- 30 Popovic, J Appl Physiol 1960;15,727-728). The rats used for the intraduodenal experiments, were also cannulated in the upper part of the duodenum. The cannulas were exteriorized at the nape of the neck. The rats were housed individually after surgery and were deprived of food, but not water,
- 35 before administration of the test substances. The same dose (4 μ mol/kg) were given iv and id as a bolus for about one minute (2 ml/kg).

Blood samples (0.1-0.4 g) were drawn repeatedly from the carotid artery at intervals up to 4 hours after given dose. The samples were frozen as soon as possible until
5 analysis of the test compound.

The area under the blood concentration vs time curve, AUC, was determined by the linear trapezoidal rule and extrapolated to infinity by dividing the last determined
10 blood concentration by the elimination rate constant in the terminal phase.

The systemic bioavailability (F%) following intraduodenal administration was calculated as

15

$$F(\%) = \frac{AUC_{id}}{AUC_{iv}} \times 100$$

20 Inhibition of Gastric Acid Secretion in the Conscious Dog.

Harrier dogs of either sex were used. They were equipped with a duodenal fistula for the administration of test compounds or vehicle and a Heidenhain-pouch for the
25 collection of gastric secretions.

Before secretory tests the animals were fasted for about 18 h but water was freely allowed. Gastric acid secretion was stimulated by a 4 h infusion of histamine dihydrochloride
30 (12 ml/h) at a dose producing about 80% of the individual maximal secretory response, and gastric juice collected in consecutive 30-min fractions. Test substance or vehicle was given iv 1 h after starting the histamine infusion, in a volume of 0.5 ml/kg body weight. The acidity of the gastric
35 juice samples were determined by titration to pH 7.0, and the acid output calculated. The acid output in the collection periods after administration of test substance or

vehicle were expressed as fractional responses, setting the acid output in the fraction preceding administration to 1.0. Percentage inhibition was calculated from fractional responses elicited by test compound and vehicle. ED_{50} -values were obtained by graphical interpolation on log dose-response curves, or estimated from single-dose experiments under the assumption of the same slope of the dose-response curve for all test compounds. All results reported are based on acid output 2 h after dosing.

10

Effect on the accumulation of ^{125}I in the thyroid gland

The accumulation of ^{125}I in the thyroid gland was studied in male, Sprague-Dawley rats which were deprived of food for 24 hours before the test. The experimental protocol of Searle, CE et al. (Biochem J 1950, 47:77-81) was followed.

Test substances suspended in 0.5% buffered (pH 9) methocel, were administered by oral gavage in a volume of 5 ml/kg body weight. After 1 hour, ^{125}I (300 kBq/kg, 3 ml/kg) was administered by intraperitoneal injection. Four hours after ^{125}I -administration, the animals were killed by CO_2 -asphyxiation and bled. The thyroid gland together with a piece of the trachea was dissected out and placed in a small test tube for the assay of radioactivity in a gamma counter (LKB-Wallac model 1282 Compugamma). Percentage inhibition was calculated according to the formula $100 (1-T/P)$, where T and P is the mean radioactivity of thyroid glands from animals treated with test agent and placebo (buffered methocel), respectively. The statistical significance for a difference between test agent- and placebo-treated animals was assessed with the Mann-Whitney U-test (two-tailed). $P < 0.05$ was accepted as significant.

35 Chemical Stability

The chemical stability of a compound of the invention is followed kinetically at low concentration at 37°C in aqueous buffer solution at different pH values. The results in Table 4 show the half life ($t_{1/2}$) at pH 7, that is the time
5 period after which half the amount of the original compound remains unchanged.

Results of biological and stability tests

- 10 Table 4 gives a summary of the test data available for the compounds of the invention.

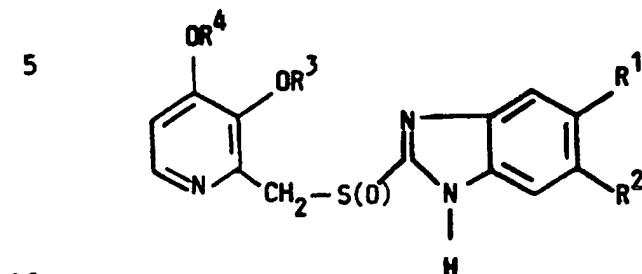
Table 4, Biological Test Data and Stability Data

Test compound Example No.	Inhibition of acid secretion iv administration ED ₅₀ µmol/kg	Bioavailability F%, Rat	Per cent inhibition of 400 µmol/kg on the uptake of ¹²⁵ I in the thyroid gland	Chemical stability a pH 7 half-life (t 1/2) min
2				42
3	0.5		0	480
4	0.74	0.9	-7	470
5		> 100	-6	270

a) 1 µmol/kg gave 14% inhibition

CLAIMS

1. Compounds of the formula I



and physiologically salts thereof wherein R^1 and R^2 , which are different, is each H, alkyl containing 1-4 carbon atoms or $-C(O)-R^5$;

15 wherein R^5 is alkyl containing 1-4 carbon atoms or alkoxy containing 1-4 carbon atoms and one of R^1 , or R^2 is always selected from the group $-C(O)-R^5$;

R^3 and R^4 are the same or different and selected from $-CH_3$,

20 C_2H_5 , $-CH_2-$ (cyclopropyl), $-CH_2-$ (cyclobutyl) and $-CH_2CH_2OCH_3$ or R^3 and R^4

together with the adjacent oxygen atoms attached to the pyridine ring and the carbon atoms in the pyridine ring form

25 a ring, wherein the part constituted by R^3 and R^4 is $-CH_2CH_2CH_2-$, $-CH_2CH_2-$ or $-CH_2$.

2. A compound according to formula I of claim 1, namely 5-carbomethoxy-6-methyl-2-[[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole.

30

3. A compound according to formula I of claim 1, namely 5-acetyl-6-methyl-2-[[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole.

35

4. A compound according to formula I of claim 1, namely 5-

acetyl-6-methyl-2-[[[3,4-propylenedioxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole.

- 5 5. A compound according to formula I of claim 1, namely 5-acetyl-6-methyl-2-[[[3,4-methylenedioxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole.
6. The sodium salt of a compound according to claim 1.
- 10 7. The sodium salt of the compound according to claim 3.
8. The magnesium salt of a compound according to claim 1.
9. A pharmaceutical composition containing as active
15 ingredient a compound according to claim 1.
10. A compound as defined in claim 1 for use in therapy.
11. A compound as defined in claim 1 for use in inhibiting
gastric acid secretion in mammals including man.
20
12. A compound as defined in claim 1 for use in the
treatment of gastrointestinal inflammatory diseases in
mammals including man.
- 25 13. A method for inhibiting gastric acid secretion by
administering to mammals including man a compound as defined
in claim 1.
14. A method for the treatment of gastrointestinal
30 inflammatory diseases in mammals including man by
administering a compound as defined in claim 1.
15. Use of a compound according to claim 1 in the
manufacture of a medicament for inhibiting gastric acid
35 secretion in mammals including man.

16. Use of a compound according to claim 1 in the manufacture of a medicament for the treatment of gastrointestinal inflammatory diseases in mammals including man.

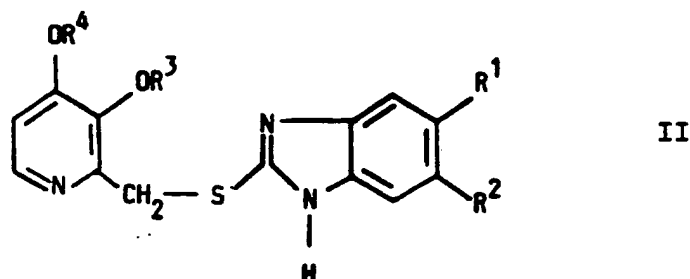
5

17. A process for the preparation of a compound of the formula I according to claim 1, by

a) oxidizing a compound of the formula II

10

15



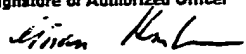
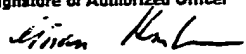
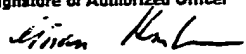
wherein R^1 , R^2 , R^3 and R^4 are as defined under formula I.

20 18. The new intermediates 2-methyl-3,4-propylenedioxy-pyridine, 2-hydroxymethyl-3,4-propylene-dioxy-pyridine, 2-methyl-3,4-methylenedioxy-pyridine, 2-hydroxymethyl-3,4-methylene-dioxypyridine, 5-acetyl-6-methyl-2-[[(3,4-propylenedioxy-2-pyridinyl)methyl]thio]-1H-benzimidazole and
25 5-acetyl-6-methyl-2-[[(3,4-methylenedioxy-2-pyridinyl)methyl]thio]-1H-benzimidazole for use in the preparation of a compound of formula I according to claim 1.

30

INTERNATIONAL SEARCH REPORT

International Application No PCT/SE 91/00416

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁶ According to International Patent Classification (IPC) or to both National Classification and IPC IPC5: C 07 D 401/12, A 61 K 31/415, 31/44																	
II. FIELDS SEARCHED <div style="text-align: center; border-top: 1px solid black; border-bottom: 1px solid black;">Minimum Documentation Searched⁷</div> <table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 30%; border-bottom: 1px solid black;">Classification System</td> <td style="border-bottom: 1px solid black;">Classification Symbols</td> </tr> <tr> <td style="height: 40px; vertical-align: bottom;">IPC5</td> <td style="vertical-align: bottom;">C 07 D</td> </tr> </table> <div style="text-align: center; border-top: 1px solid black; border-bottom: 1px solid black;">Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in Fields Searched⁸</div> <p>SE,DK,FI,NO classes as above</p>			Classification System	Classification Symbols	IPC5	C 07 D											
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IPC5	C 07 D																
III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹ <table style="width: 100%; border-collapse: collapse;"> <tr> <th style="width: 10%; border-bottom: 1px solid black;">Category *</th> <th style="width: 60%; border-bottom: 1px solid black;">Citation of Document,¹¹ with indication, where appropriate, of the relevant passages¹²</th> <th style="width: 30%; border-bottom: 1px solid black;">Relevant to Claim No.¹³</th> </tr> <tr> <td style="text-align: center; vertical-align: top;">A</td> <td>US, A, 4359465 (THE UPJOHN COMPANY) 16 November 1982, see the whole document --</td> <td style="text-align: center; vertical-align: top;">1-12,15-17</td> </tr> <tr> <td style="text-align: center; vertical-align: top;">A</td> <td>US, A, 4255431 (AKTIEBOLAGET HÄSSLE) 10 March 1981, see the whole document --</td> <td style="text-align: center; vertical-align: top;">1-12,15-17</td> </tr> <tr> <td style="text-align: center; vertical-align: top;">A</td> <td>EP, A, 0197013 (AKTIEBOLAGET HÄSSLE) 8 October 1986, see the whole document --</td> <td style="text-align: center; vertical-align: top;">1-12,15-17</td> </tr> <tr> <td style="text-align: center; vertical-align: top;">A</td> <td>EP, A, 0208452 (TAKEDA CHEMICAL INDUSTRIES, LTD) 14 January 1987, see the whole document -- -----</td> <td style="text-align: center; vertical-align: top;">1-12,15-17</td> </tr> </table>			Category *	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³	A	US, A, 4359465 (THE UPJOHN COMPANY) 16 November 1982, see the whole document --	1-12,15-17	A	US, A, 4255431 (AKTIEBOLAGET HÄSSLE) 10 March 1981, see the whole document --	1-12,15-17	A	EP, A, 0197013 (AKTIEBOLAGET HÄSSLE) 8 October 1986, see the whole document --	1-12,15-17	A	EP, A, 0208452 (TAKEDA CHEMICAL INDUSTRIES, LTD) 14 January 1987, see the whole document -- -----	1-12,15-17
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A	EP, A, 0197013 (AKTIEBOLAGET HÄSSLE) 8 October 1986, see the whole document --	1-12,15-17															
A	EP, A, 0208452 (TAKEDA CHEMICAL INDUSTRIES, LTD) 14 January 1987, see the whole document -- -----	1-12,15-17															
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>* Special categories of cited documents:¹⁰</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p> </div> </div>																	
IV. CERTIFICATION <table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%; border-bottom: 1px solid black;">Date of the Actual Completion of the International Search</td> <td style="width: 50%; border-bottom: 1px solid black;">Date of Mailing of this International Search Report</td> </tr> <tr> <td style="text-align: center;">11th September 1991</td> <td style="text-align: center;">1991 -09- 1 9</td> </tr> <tr> <td style="border-bottom: 1px solid black;">International Searching Authority</td> <td style="border-bottom: 1px solid black;">Signature of Authorized Officer</td> </tr> <tr> <td style="text-align: center;">SWEDISH PATENT OFFICE</td> <td style="text-align: center;">  Göran Karlsson </td> </tr> </table>			Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	11th September 1991	1991 -09- 1 9	International Searching Authority	Signature of Authorized Officer	SWEDISH PATENT OFFICE	 Göran Karlsson							
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SWEDISH PATENT OFFICE	 Göran Karlsson																

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. ☒ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE ¹

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☒ Claim numbers 13-14, because they relate to subject matter not required to be searched by this Authority, namely:

A method for treatment of the human or animal body by therapy,
see rule 39.1.

2. ☐ Claim numbers _____, because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claim numbers _____, because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING ²

This International Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.
2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:
3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:
4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

- ☐ The additional search fees were accompanied by applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.PCT/SE 91/00416**

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the Swedish Patent Office EDP file on **91-07-31**
The Swedish Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A- 4359465	82-11-16	DE-A- 3176664	88-04-07
		EP-A-B- 0045200	82-02-03
		JP-B- 1060008	89-12-20
		JP-C- 1574094	90-08-20
		JP-A- 57053406	82-03-30
US-A- 4255431	81-03-10	AT-B- 374471	84-04-25
		AT-B- 374472	84-04-25
		AT-B- 374473	84-04-25
		AT-B- 375365	84-07-25
		AT-B- 389995	90-02-26
		AU-B- 529654	83-06-16
		AU-D- 4602779	79-10-18
		CA-A- 1127158	82-07-06
		CA-A- 1129417	82-08-10
		EP-A-B- 0005129	79-10-31
		JP-C- 1312930	86-04-28
		JP-C- 1504537	89-07-13
		JP-A- 54141783	79-11-05
		JP-A- 58192880	83-11-10
		JP-B- 60034956	85-08-12
		JP-B- 63053191	88-10-21
		SE-A- 7804231	79-10-15
		US-A- 4337257	82-06-29
		US-A- 4508905	85-04-02
EP-A- 0197013	86-10-08	JP-A- 61205211	86-09-11
EP-A- 0208452	87-01-14	JP-A- 62116576	87-05-28
		US-A- 4738975	88-04-19